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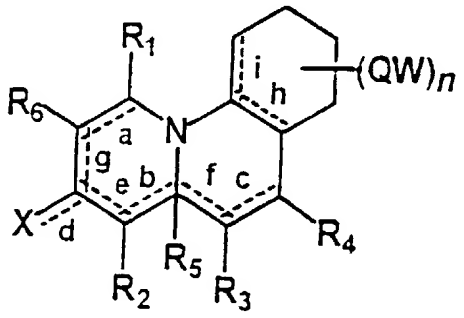
(54) Benzo (C)quinolizine derivatives, their preparation and use as 5-alphareductases inhibitors

(57) The present invention refers to benzo[c]quinolizines derivatives, fully and partially saturated, having formula (I)



(I)

and their pharmaceutically acceptable salts which proves useful for pharmaceutical and agricultural use being capable of inhibiting the 5α-reductase enzyme either selectively in respect of 5αR-I and 5αR-II or on both the iso-enzymes. Compounds (1) can be used to regulate growth and act as herbicides, or to treat acne, baldness, prostatic cancer and prostatic hypertrophy.

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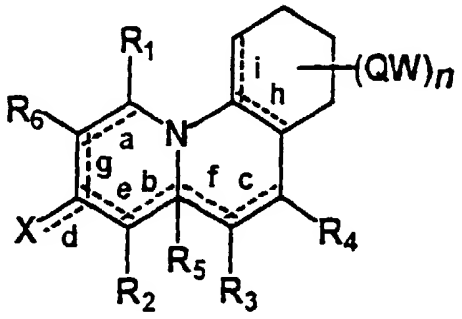
Description

[0001] The present invention refers to fully and partially saturated benzo[c]-quinolizine derivatives of general formula (I) their pharmaceutically acceptable salts or esters, processes for their preparation and composition for pharmaceutical and agricultural use containing them.

Field of the invention

[0002] The present invention refers to benzo[c]quinolizine derivatives of general formula (I) wherein:



(I)

R_1, R_2 R_3, R_4, R_6, same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide, NRR', C_{1-8}alkylamino, arylamino, C_{1-8}alkyloxy, aryloxy, COOR, CONRR', C(=O)R wherein R and R', same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl;
R_5 is chosen in the group consisting of: H, C_{1-8}alkyl, C_{1-8}alkylaryl, COOR, CN, aryl, heterocycle, C_{1-8}alkyl-heterocycle; C_{1-8}alkyl-heterocycle-ribose-phosphate X is chosen in the group consisting of: O, C(=O)R, COOR, NO_2, CONR'R wherein R and R' are as above defined;
Q is chosen in the group consisting of: simple bond, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined;
W is chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8} alkenyl, C_{2-8}alkinyl, cycloalkyl, trifluoromethyl, C_{1-8}alkoxy, C_{1-8} alkoxy-C_{1-8}alkyl, arylC_{1-8}alkyl, aryl, aryloxy, arylamino, C_{1-8}alkylcarbonyl, arylcarbonyl, arylcarboxyl, arylcarboxyamide, halogen, CN, NRR', C_{1-8}alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkinyl, cycloalkyl, aryl, heterocycle, can be substitued; n is an integer comprised between 1 and 4;
the symbol ----- means that the corresponding bonds a, b, c, d e, f, g, h and i can be a simple or a double bond; with the proviso that when b or f are a double bond then the group R_5 is absent;
their pharmaceutically acceptable salts or esters, their process of preparation and their use as inhibitors of steroid 5α-reductases.

State of the art

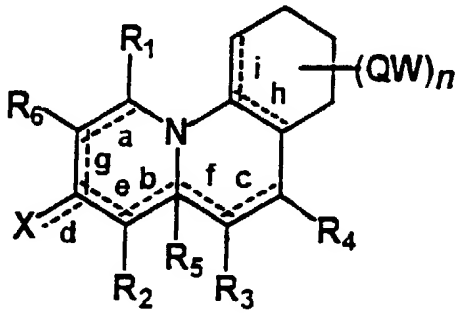
[0003] The enzyme known as steroid 5α-reductase (hereinafter indicated as 5α-reductase) is a system formed by two iso-enzymes (type I and type II or 5αR-I and 5αR-II respectively) which converts testosterone into dihydrotestosterone, the most powerful androgen circulating in the body. The type I iso-enzyme (5αR-I) is mainly present in liver and skin while the type II iso-enzyme (5αR-II) is mainly present in the prostate tissue and in the male sexual organs and its activity is essential in the fetal developping process for the differentiation of the external sexual organs. The production of dihydrotestosterone is associated with some pathologies which are widely diffused as for example benign prostate hypertrophy, prostate cancer, baldness and acne in men and hirsutism in women. More particularly iso-enzyme I plays a role in the pathologies regarding the skin while iso-enzyme-II is involved in prostate pathologies. In the recent years a lot of international searchers have tried to isolate new compounds capable of inhibiting the 5α-reductase enzyme in order to treat the above said pathologies, especially, if possible, acting selectively on only one of the two iso-enzymes. Inhibitors of 5α-reductase, and also of the iso-enzymes 5αR-I and 5αR-II were already described [see for example J.Med.Chem. 36, 4313-15 (1993), J.Med.Chem. 37, 3871-74 (1994), J.Med.Chem. 40, 1112 (1997) J.Med.Chem. 40,

3466 (1997)]; for example finasteride was used with success in the treatment of benign prostate hypertrophy. It is therefore evident the importance of developping new compounds capable of inhibiting the action of the 5α-reductase enzyme and in particular capable of acting selectively on 5αR-I iso-enzyme which, as said, is responsible, of widely diffused pathologies having an high impact as baldness in men and hirsutism in women.

[0004] Moreover it was also found, an it is another object of the present invention, that the compound of formula (I) can inhibit steroid 5α-reductase enzymes in plants and therefore can selectively regulate the plant growth in light and dark conditions. The compounds according to the present invention can be used as phyto-pharmaceuticals in agricolture permitting to improve the morphogenesis and development of commercially useful plants or as herbicides capable of inhibiting the growth of infesting plants.

Detailed description of the invention

[0005] The present invention refers to new compounds capable of inhibiting the 5α-reductase enzyme, either selectively in respect of 5αR-I and 5αR-II or on both the iso-enzymes, useful for the treatment of the pathologies mediated by the enzyme or for agricoltural uses as plant growth regulators or herbicides. The products according to the invention have general formula



(I)

wherein the substituents R_1, R_2, R_3, R_4, R_5, R_6, X, Q, W, n and the symbol - ----- are as above defined.

[0006] According to the present invention with group C_{1-8}alkyl, C_{2-8} alkenyl and C_{2-8}alkinyl are indicated linear or branched alkyl radicals as for example: methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, heptyl, octyl, ethylene, propene, butene, isobutene, acetylene, propine, butine ecc.

[0007] With cycloalkyl are indicated: cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, cyclooctane, norbornane, canphane, adamantane. With aryl are indicated: phenyl, biphenyl and naphtyl.

[0008] Heterocycle means in particular: saturated or aromatic heterocycles containing one or more N atoms, more particularly: pyridine, imidazole, pyrrole, indole, triazoles, pyrrolidine, pyperidine.

[0009] Phosphate means the anion of mono-, di- or triphosphoric acid

[0010] Halogen means: fluorine, chlorine, bromine, iodine.

[0011] The substituents of the above said group W are preferably: halogen, OR, phenyl, NRR', CN, COOR, CONRR', C_{1-8}alkyl (wherein R and R' are as above defined).

[0012] In particular, according to the present invention compounds of formula (I) are preferred wherein:

R_5 = H, C_{1-8}alkylaryl, COOR, CN, aryl, heterocycle, C_{1-8}alkyl-heterocycle; or a group C_{1-8}alkyl-heterocycle-ribose-phosphate

X = O, COOH

Q = simple bond, CO, CONR, NR (wherein R is as above defined) W = H, F, Cl, Br, Me, t-butyl, C_{1-8}alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8}alkyl, C_{1-8} alkylcarbonyl, phenylcarbonyl.

n = 1 and 2

R_1, R_2, R_3, R_4, R_6 = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined). Among the pharmaceutically acceptable esters and salts according to the present invention the following can be mentioned: hydrochloride, sulphate, citrate, formiate, phosphate.

[0013] Preferred compounds according to the present invention are:

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)benzo[c]quinolizin-3-one;
8-chloro-2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4-dimethyl-(1H)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a$_1$7,8,9,10,10a-decahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
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3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
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8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
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2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
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8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
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8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
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3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
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8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;
8-chloro-5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-8-methyl-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;
8-chloro-5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-4,8-dimethyl-(3*H*)-benzo[c]quinolizin-3-one;
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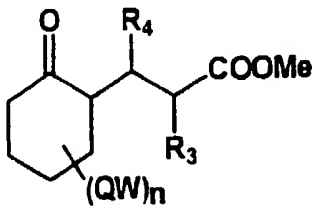
8-chloro-2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,7,8,9,10-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;

Dodecahydro-benzo[c]quinolizin-3-ones and decahydro-benzo[c]quinolizin-3-ones according to the present invention, wherein the double bonds i and h are absent, can be prepared as shown in Scheme 1, according to the general preparation of benzo[c]quinolizine-3-ones already reported in the patent WO 97/29107; in particular, for example, starting from compounds of formula 2



(2)

wherein R_3, R_4, W, Q and n are as above defined.

[0014] The compounds 2 are commercialy available or can be prepared according to known techniques.

[0015] As it can be seen from the Scheme 1 the preparation of the compounds according to the invention involves the cyclization of the ester 2 to the enamide 3 by heating at 120°C compounds 2 in formic acid in the presence of ammonium hydrogencarbonate. The enamide 3 is reduced to the *trans*-fused amide 4 for example with sodiumcyanoborohydride at pH 4, followed by the protection of the amide-group with a protecting group, for example tert-butoxycarbonyl (t-Boc), to give compound 5; compound 5 is reduced to compound 6, for example (when R_5 is H) with sodium borohydride in ethanol (pH 4), which is reacted with a silyloxydiene 8, produced "in situ" starting from vinyl-ketones 7 (wherein R_1, R_2 and R_6 are as above defined) with a silylating agent as trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and thereafter hydrolized, for example in sodium hydrogencarbonate, to give the compounds of formula (I) wherein X = O. The possible introduction of the double bonds and the transformation of the group X in one of the other groups mentioned above can be easily performed according to known techniques starting from the corresponding compound of formula (I) obtained as indicated. For example the introduction of the double bonds in position a or/and b, can be performed by reaction of dichlorodicyanoquinone (DDQ) with the corresponding silylenolethers or by oxidation with mercuric acetate of the saturated corresponding compound obtained as described above. The transformation of group X can be performed via the corresponding enoltriflates and their carbonylation in the presence of palladium diacetate, triphenylphosphine and the suitable nucleophilic reagent (alcohol, amine, nitro-group).

[0016] The compounds according to the present invention wherein the double bonds i or h and b are present, can be prepared as shown in Scheme 2, for example starting from the above said compounds of formula 2.

[0017] The key step of the process is the thermal rearrangement-cyclization of the isoxazoline-5-spirocyclopropane 14 to final product 1. This process has been already applied for the synthesis of other nitrogen bridgehead polycylic compounds as reported in *J. Org. Chem.* 1988, *53*, 2426 and in *J. Med. Chem.* 1997, *40*, 1112.

[0018] As it can be seen from the Scheme 2 the preparation of the compounds according to the invention involves protection of the carbonyl of compound 2 (wherein R_3 and R_4 are as above defined) as a ketal, for example with ethylenglicole under acid catalysis, followed by the selective reduction of the ester group in compound 9 to aldehyde 10, for example by DIBAL at -78 °C. The transformation of the aldehyde 10 to oxime 11, made for example by reaction with hydroxylamine hydrochloride in pyridine, is followed by cycloaddition to methylenecyclopropane 12 (wherein R_1, R_2, R_6 are as above defined) of the *in situ* generated nitrile oxide by reaction of oxime 11 with sodium hypochlorite and triethylamine. The isoxazoline-5-spirocyclopropane 13 is then deprotected under acid catalysis and submitted to thermal rearrangement in boiling DMF for 3-6 hrs to give compounds 1.

[0019] Octahydrobenzo[c]quinolizin-3-ones of formula 1, wherein R_1, R_2, R_3, R_4, R_6 are H, QW is H or $-CH_2CONHtBu$ (at position 8), n = 1 and both the double bonds b and h (or i) are present can be prepared for example starting from compound 2 wherein R_3, R_4, are H and QW is H or 5-(N-*t*-butyl)acetamido and n = 1.

Example 1

Preparation of methyl 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanoate.
[compound 9 wherein $(QW)_n$ = H, R_3 = R_4 = H]

[0020] In a flask provided with a Dean-Stark apparatus, methyl ester 2 (20.0 g, 109 mmol), ethylenic glycol (60 mL, 1.08 mol) and *p*-TsOH (0.8 g, 5 mmol) were dissolved in toluene (550 mL) and the resulting solution was heated under reflux. After 4 h the reaction was complete and the mixture was washed with $NaHCO_3$ 2 N, water and dried over Na_2SO_4. After filtration and evaporation of the solvent, a crude yellow oil was obtained. This was purified by distillation under reduced pressure, affording pure 9 [15.9 g, 64%, bp 127-130 °C (2 mbar)].

Example 2

Preparation of 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanal [compound 10 wherein $(QW)_n$ = H, R_3 = R_4 = H]

[0021] To a solution of 9 (15.7 g, 69.1 mmol) in toluene (220 mL) cooled at - 78 °C, DIBAL-H (1.2 M solution in toluene, 116 mL, 135 mmol) was slowly added during 3 h. After 3 h of stirring, the mixture was poured into water (110 mL) and allowed to warm to room temperature. After filtration on a Celite layer, the organic phase was dried over Na_2SO_4. After filtration and evaporation of the solvent the residual crude oil was purified by chromatography (petroleum ether-EtOAc, 2:1, R_f0.30), affording pure aldehyde 10 as oil (6.6 g, 48%).

Example 3.

Preparation of 3-[2-(1,3-dioxolan-2-yl)cyclohexyl]propanal oxime [compound 11 wherein $(QW)_n$ = H, R_3 = R_4 = H].

[0022] A solution of aldehyde 10 (6.12 g, 31.0 mmol) and $NH_2OH \cdot HCl$ (2.76 g, 40.0 mmol) in pyridine (120 mL) was stirred for 2 h at room temperature. The mixture was extracted with Et_2O and the organic layer washed with water and dried over Na_2SO_4. After filtration and evaporation of the solvent the crude oil obtained was purified by chromatography (petroleum ether- EtOAc, 1.5:1, R_f 0.5). Recrystallization from Et_2O-petroleum ether gave pure oxime 11 (4.02 g, 61%, mp 74-75 °C) as a 1:1 mixture of E,Z diastereoisomers.

Example 4

Preparation of 6-[2-[2-(1,3-dioxolan-2-yl)cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 13 wherein $(QW)_n$ = H, R_1 = R_2 = R_3 = R_4 = R_6 = H].

[0023] Liquid methylenecyclopropane [compound 12 wherein R_1 = R_2 = R_6 = H] (5 mL) was transferred by a double-tipped needle into a solution of oxime 11 (4.02 g, 18.8 mmol) and Et_3N (226 mg, 2.23 mmol) in CH_2Cl_2 (35 mL) cooled at -60 °C. The mixture was allowed to warm to 0 °C and NaClO (8% solution, 54 mL) was slowly added in 3.5 h. The solution was stirred for 21 h, then the phases were separated, the aqueous layer was extracted with CH_2Cl_2 (3 x 25 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude 13 (4.89 g, 73%) was obtained and used without purification in the next reaction.

Example 5

Preparation of 6-[2-(2-oxocyclohexyl)ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 14 wherein $(QW)_n$ = H, R_1 = R_2 = R_3 = R_4 = R_6 = H].

[0024] Isoxazoline 13 (3.64 g, 13.7 mmol) and *p*-TsOH (392 mg, 2.23 mmol) were dissolved in acetone (90 mL) and water (30 mL) and the resulting solution was stirred at room temperature for 7 days. The product was extracted with CH_2Cl_2, the organic phase washed with $NaHCO_3$ (2 N) and dried over Na_2SO_4. After filtration and evaporation of the solvent, a yellow crude oil (2.36 g) was obtained. This was purified first by chromatography (CH_2Cl_2-EtOAc, 12.5:1, R_f 0.35) and then by recrystallization from Et_2O-petroleum ether, affording pure isoxazoline 14 (1.43 g, 47%, mp 109 °C).

Example 6

Preparation of 2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one [compound 1 wherein $(QW)_n$ = H, R_1 = R_2 = R_3 = R_4 = R_6 = H and h = double bond].
and 2,3,5,6,6a,7,8,9-octahydro-(3*H*)-benzo[c]quinolizin-3-one [compound 1 wherein $(QW)_n$ = H, R_1 = R_2 = R_3 = R_4 = R_6 = H and i = double bond].

[0025] Isoxazoline 14 (476 mg, 2.15 mmol) dissolved in dry DMF (50 mL) was heated under reflux for 3 h. After distillation of the solvent, a yellow crude oil (470 mg) was obtained, containing a mixture of rearrangement products. This oil was purified by chromatography (CH_2Cl_2-MeOH, 20:1), affording pure 1 (163 mg, 37%, R_f 0.36, oil) as 10:1 mixture of the two isomers having the double bond in position h or i respectively.

Example 7

Preparation of methyl 3-[[2-(1,3-dioxolan-2-yl)-5-(N-*t*-butyl)acetamido]cyclohexyl]]propanoate [compound 9 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R_3 = R_4 = H]

[0026] Prepared as in example 1. Starting from compound 2 [wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, R_3 = R_4 = H] (32.14 g, 108 mmol), crude ketal 9 (22.2 g, 60%) was obtained as an oil. A portion (100 mg) of this crude oil was purified by chromatography (CH_2Cl_2-MeOH, 30:1, 1% Et_3N, R_f 0.31, oil), affording 9 as a mixture of *cis* and *trans* isomers.

Example 8

Preparation of 3-[[2-(1,3-dioxolan-2-yl)-5(*N*-*t*-butyl)acetamido]cyclohexyl]]propanal oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$]

[0027] A solution of ketal [compound 9 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$] (22.1 g, 64.7 mmol) in toluene (500 mL) was cooled at -78 °C; DIBAL-H (solution 1 M in toluene, 288 mL) was then slowly added in 4 h and the resulting solution was stirred for 3 h. After addition of water (260 mL), the mixture was allowed to warm to room temperature, extracted with CH_2Cl_2 (4 x 200 mL) and the organic layer dried over Na_2SO_4. After filtration and evaporation of the solvent a crude oil (17.2 g) was obtained, used without purification for the next step.

[0028] Then, under stirring, to a solution of distilled oxalyl chloride (10.9 mL, 125 mmol) in CH_2Cl_2 (270 mL), cooled at -60 °C, DMSO (15 mL, 211 mmol) was added, followed by slow addition (25 min) of a solution of the above crude oil in CH_2Cl_2 (260 mL). After 15 min, Et_3N (56 mL) was slowly added in 15 min. After 5 min stirring, the mixture was warmed to room temperature and washed with water (535 mL); after separation of the phases, the aqueous one was extracted with CH_2Cl_2 (3 x 250 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the aldheyde [compound 10 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$] was obtained as a crude oil (14.6 g), used without purification for the next reaction.

[0029] A solution of this aldheyde (14.6 g) in pyridine (210 mL) was added to a solution of $NH_2OH \cdot HCl$ (13.7 g, 196.9 mmol) in pyridine (107 mL) and the resulting mixture was stirred at room temperature for 20 h. The mixture was poured into CH_2Cl_2 (800 mL) and washed with water; after separation of the phases, the aqueous one was extracted with CH_2Cl_2 (3 x 200 mL) and the combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, crude oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$] (11.3 g) was obtained. This was purified by chromatography eluting with $CHCl_3$-MeOH, 50:1, 1% Et_3N, and then with $CHCl_3$-MeOH, 3:1, 1% Et_3N (R_f 0.32), affording pure oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$] (7.41 g, 35%, oil) as a 1:1 mixture of *E/Z* diastereoisomers

Example 9

Preparation of 6-[2-[2-(1,3-dioxolan-2-yl)-5-(*N*-*t*-butyl)acetamido]cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 13 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$]

[0030] Prepared as example 4. Starting from the above prepared oxime [compound 11 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_3 = R_4 = H$] (7.40 g, 22.6 mmol), isoxazoline [compound 13 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$] (4.96 g, 58%) was obtained as a crude oil used without purification in the next reaction.

Example 10

Preparation of 6-[2-[2-oxo-5-[(*N*-*t*-butyl)acetamido]cyclohexyl]ethyl]-4-oxa-5-azaspiro[2.4]hept-5-ene [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$].

[0031] Crude isoxazoline 13 [wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$] (4.92 g, 13.1 mmol) was dissolved in acetone (150 mL) and H_2SO_4 (1.7 M solution in acetone, 9.8 mL) was slowly added, under vigorous stirring, at room temperature. When the reaction was complete, Na_2CO_3 was added up to pH 7; after filtration and evaporation of the solvent, crude 14 was obtained. This was purified by chromatography, eluting with CH_2Cl_2-MeOH, 60:1 and then 20:1 (R_f 0.28), affording pure 14 as an oil [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$] (1.45 g, 33%) as a mixture of *cis* and *trans* isomers.

Example 11

Preparation of 2,3,5,6,7,8,9,10-octahydro-(1*H*)-8-(*N*-*t*-Butyl)acetamido-benzo[c]quinolizin-3-one [compound 1 wherein (QW)= 8-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$ and h = double bond] and 2,3,5,6,6a,7,8,9-octahydro-(1*H*)-8-(*N*-*t*-Butyl)acetamido-benzo[c]quinolizin-3-one [compound 1 wherein (QW)= 8-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$ and i = double bond].

[0032] A solution of isoxazoline [compound 14 wherein (QW)= 5-(*N*-*t*-butyl)acetamido n = 1, $R_1 = R_2 = R_3 = R_4 = R_6 = H$] (947 mg, 2.83 mmol) in DMF (109 mL) was heated under reflux for 3 h. After distillation under reduced pressure of the solvent a crude oil containing a mixture of rearrangement products was obtained. Chromatographic separation

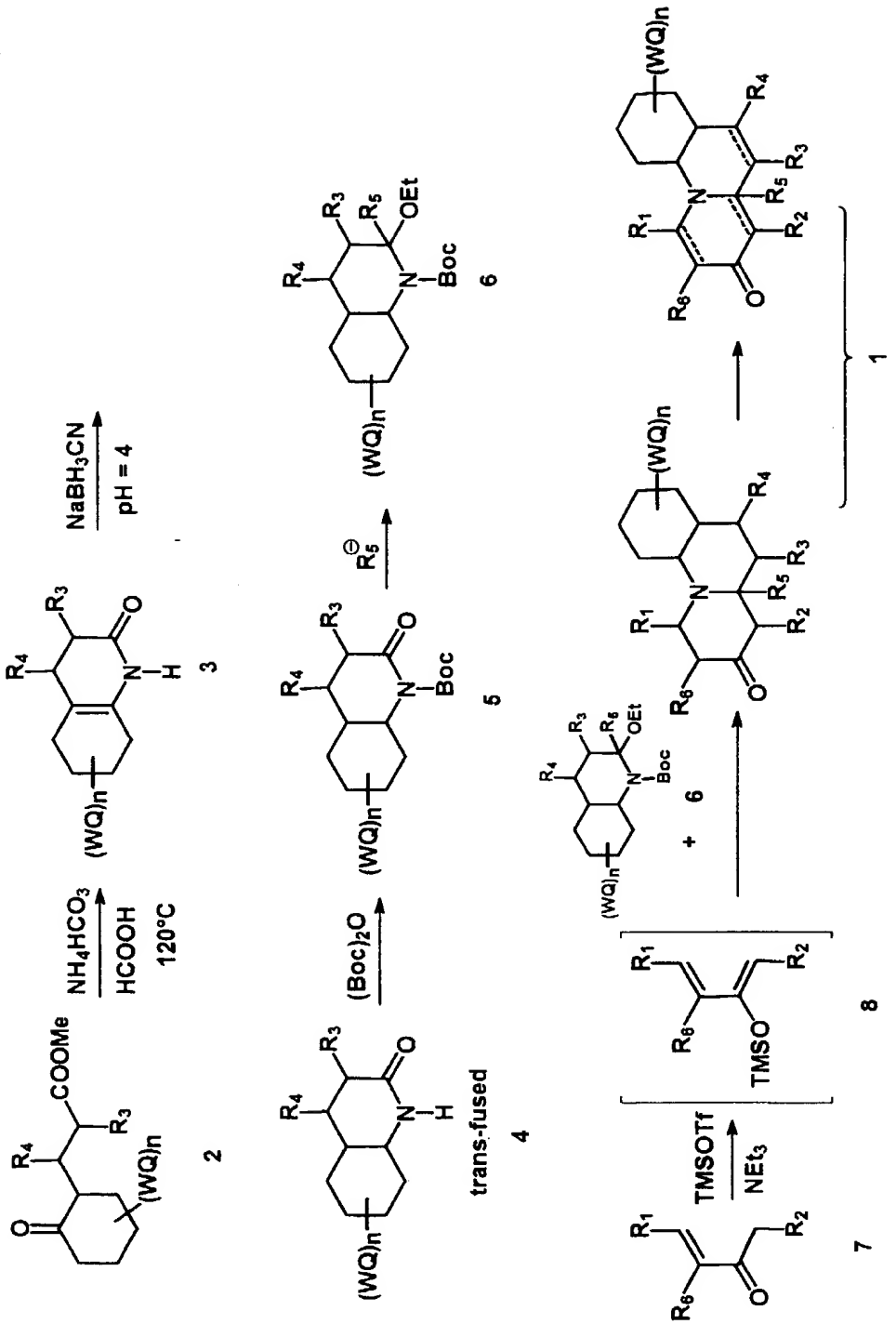
(CH_2Cl_2-MeOH, 25:1, 1 % NH_3) afforded pure 1 (161 mg, 18%, R_f 0.32, oil) as 10:1 mixture of the two isomers having the double bond in position h or i respectively.

Activity Test

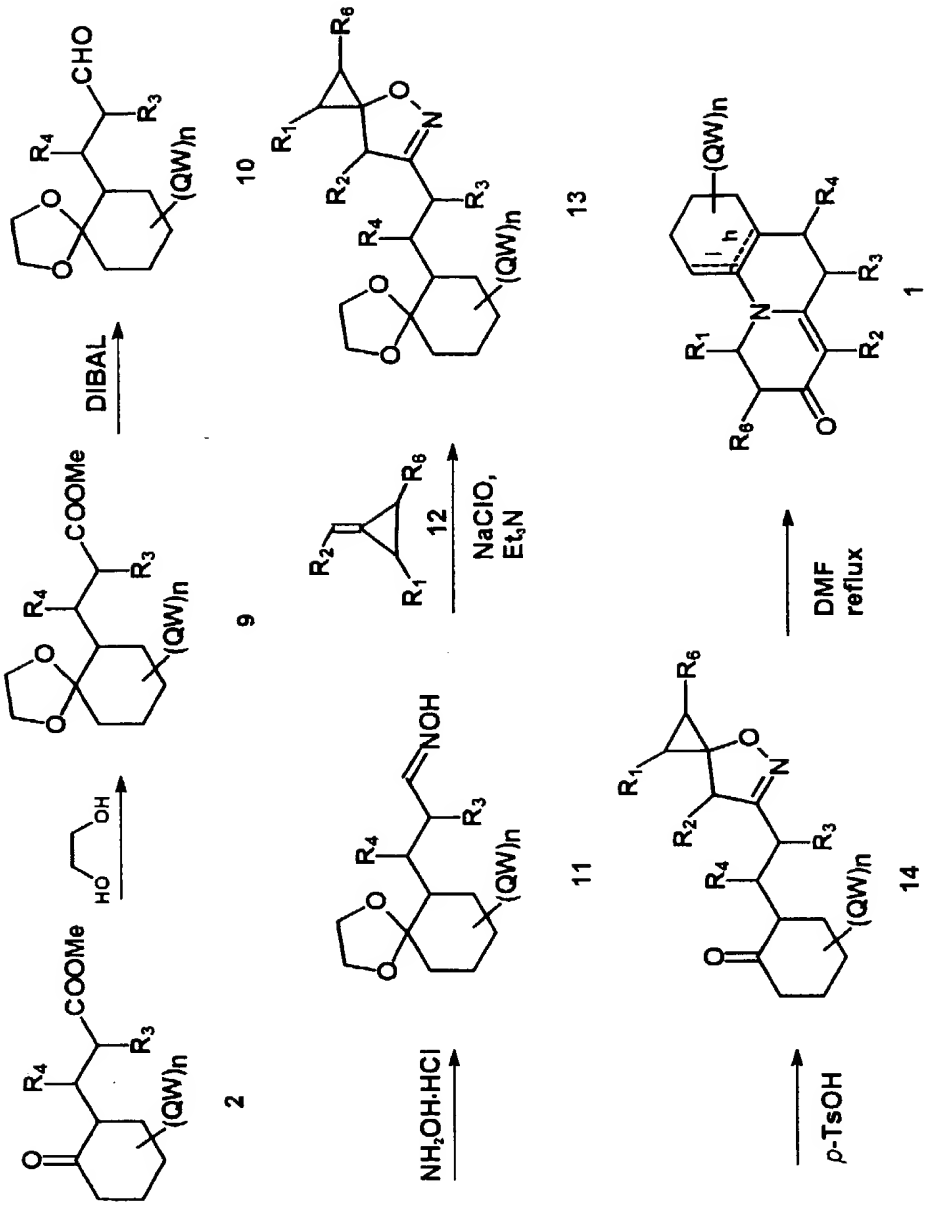
[0033] The inhibition potency of the prepared compounds in respect of the iso-enzymes 1 and 2 of 5α-reductase was determined using cellular systems (for example CHO cells) expressing human iso-enzymes 2 and 1. The samples are incubated in the presence of testosterone labelled with tritium and thereafter the quantity of labelled dihydrotestosterone formed in the absence and in the presence of the inhibitor is measured. The compounds showed high inhibiting power of 5α-reductase enzyme (in particular of iso-enzyme 1) with an inhibition higher than 50% at the concentration of 10 - 100 nM.

[0034] For example the 10:1 mixture of 2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one [compound 1 wherein $(QW)_n$ = H, $R_1 = R_2 = R_3 = R_4 = R_6$ = H and h = double bond] and 2,3,5,6,6a,7,8,9-octahydro-(3*H*)-benzo[c]quinolizin-3-one [compound 1 wherein $(QW)_n$ = H, $R_1 = R_2 = R_3 = R_4 = R_6$ = H and i = double bond], prepared according the example 6, was as selective inhibitor towards type 1 isoenzyme, having an IC_{50} value of 58 nM, whereas the IC_{50} towards the type 2 isoenzyme was not determinable.

[0035] For the therapeutical administration the compounds according to the invention are prepared in the form of pharmaceutical compositions containing the active principle and the organic or inorganic excipients suitable for the oral, parenteral or topic administration of the compositions. The pharmaceutical compositions can thererfore be in the solid form (dragees, suppositories, creams, ointments), liquid form (solutions, suspensions, emulsions) and can possibly contain the stabilizers, conservatives, humectants, emulsifier, buffers or salts used for equilibrating the osmotic pressure which are commonly used in the art. Generally the administration of the compounds is performed according to the modalities and quantities observed for the known agents used for the same purposes and taking into consideration the age and conditions of the patients.


NaBH3CN
pH = 4
NH4HCO3
HCOOH
120°C
(Boc)2O
trans-fused
TMSOTf
NEt3
+ 6
Boc
OEt
TMSO
(WQ)n

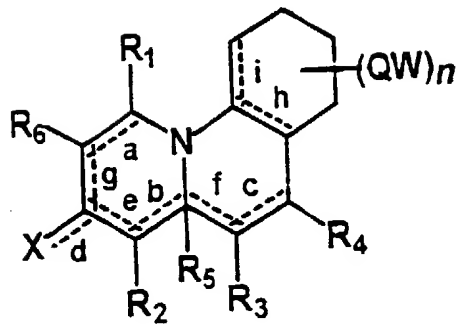
Scheme 1



Scheme 2

Claims

1. Fully and partially reduced benzo[c]-quinolizine compounds of formula (I) wherein:



(I)

R_1, R_2, R_3, R_4, R_6, same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, aryl, heterocycle, halogen, CN, azide, NRR', C_{1-8}alkylamino, arylamino, C_{1-8}alkyloxy, aryloxy, COOR, CONRR', C(=O)R, wherein R and R', same or different, are chosen in the group consisting of: H, C_{1-8}alkyl, cycloalkyl, aryl, heterocycle, arylC_{1-8}alkyl;
R_5 is chosen in the group consisting of: H, C_{1-8}alkyl, C_{1-8}alkylaryl, COOR, CN, aryl, heterocycle, C_{1-8}alkyl-heterocycle; C_{1-8}alkyl-heterocycle-ribose-phosphate X is chosen in the group consisting of: O, C(=O)R, COOR, NO_2, CONR'R wherein R and R' are as above defined;
Q is chosen in the group consisting of: simple bond, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkinyl, cycloalkyl, CO, CONR, NR, wherein R is as above defined;
W is chosen in the group consisting of: H, C_{1-8}alkyl, C_{2-8} alkenyl, C_{2-8}alkinyl, cycloalkyl, trifluoromethyl, C_{1-8}alkoxy, C_{1-8} alkoxy-C_{1-8}alkyl, arylC_{1-8}alkyl, aryl, aryloxy, arylamino, C_{1-8}alkylcarbonyl, arylcarbonyl, arylcarboxyl, arylcarboxyamide, halogen, CN, NRR', C_{1-8}alkylamino, heterocycle wherein the groups alkyl, alkenyl, alkinyl, cycloalkyl, aryl, heterocycle, can be substitued; n is an integer comprised between 1 and 4;
the symbol ----- means that the corresponding bonds a, b, c, d e, f, g, h and i can be a simple or a double bond;
with the proviso that when b or f are a double bond then the group R_5 is absent;
their pharmaceutically acceptable salts and esters.

2. Benzo[c]-quinolizine compounds of formula (I) according to Claim 1, wherein

R_5 = H, C_{1-8}alkylaryl, COOR, CN, aryl, heterocycle, C_{1-8}alkyl-heterocycle; or a group C_{1-8}alkyl-heterocycle-ribose-phosphate
X = O, COOH
Q = simple bond, CO, CONR, NR (wherein R is as above defined) W = H, F, Cl, Br, Me, t-butyl, C1-8alkoxy, 2,5-dimethylhexyl, trifluoromethyl, 2,5-(di-trifluoromethyl)-phenyl, 4-methoxy-phenyl, 4-fluoro-phenyl, phenyl, phenyl-C_{1-8}alkyl, C_{1-8} alkylcarbonyl, phenylcarbonyl.
n = 1 and 2
R_1, R_2, R_3, R_4, R_5, R_6 = H, Me, CN, phenyl, COOR, CONRR' (wherein R and R' are as above defined).

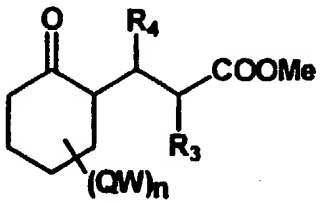
3. Benzo[c]-quinolizine compounds according to Claim 1 of formula :

2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,4,4a,5,6,6a,7,8,9,10,10a-dodecahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;

2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-6-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-6,8-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6-dimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-5,6,8-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;

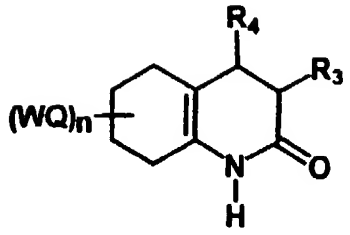
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9,10,10a-decahydro-1,4,5,6-tetramethyl-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6-trimethyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1,5,6,8-tetramethyl-(4a*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;
8-chloro-5,6,6a,7,8,9,10,10a-octahydro-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-8-methyl-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;
8-chloro-5,6,6a,7,8,9,10,10a-octahydro-4-methyl-(3*H*)-benzo[c]quinolizin-3-one;
5,6,6a,7,8,9,10,10a-octahydro-4,8-dimethyl-(3*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,7,8,9,10-octahydro-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,7,8,9,10-octahydro-8-methyl-(1*H*)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9-octahydro-(1H)-benzo[c]quinolizin-3-one;
8-chloro-2,3,5,6,6a,7,8,9-octahydro-(1H)-benzo[c]quinolizin-3-one;
2,3,5,6,6a,7,8,9-octahydro-8-methyl-(1H)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
4a-benzyl-3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
8-chloro-3,4,5,6,6a,7,8,9,10,10a-decahydro-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-8-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-4-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;
3,4,5,6,6a,7,8,9,10,10a-decahydro-1-methyl-4a-(4-pyridyl)methyl-(4a*H*)-benzo[c]quinolizin-3-one;

4. Process for the preparation of compounds according to Claim 1 wherein: the ester-group of a compound of formula (2)



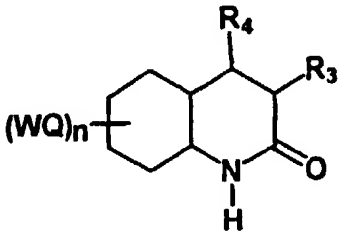
(2)

(wherein R_3, R_4 and $(WQ)_n$ are as defined in Claim 1)
is cyclized to enamide (3)



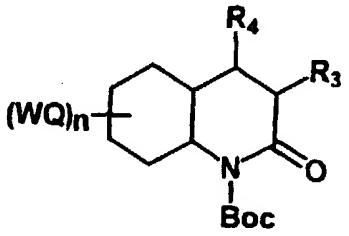
(3)

(wherein R_3, R_4 and $(WQ)_n$ are as defined in Claim 1)
which is reduced to the amide (4)



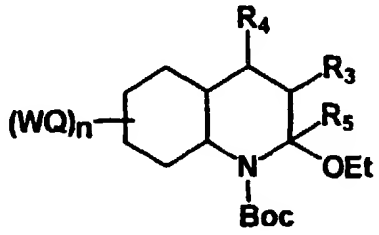
(4)

(wherein R_3, R_4 and $(WQ)_n$ are as defined in Claim 1)
which is protected with a protecting group Boc to give the compound (5)



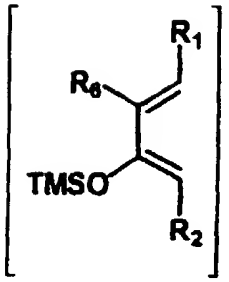
(5)

(wherein R_3, R_4 and $(WQ)_n$ are as defined in Claim 1)
which is reduced to compound (6) with sodium borohydride in ethanol (pH4)



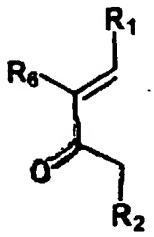
(6)

(wherein R_3, R_4, R_5 and $(WQ)_n$ are as defined in Claim 1)
and compound (6) is reacted with a silylether (8)



(8)

(wherein R_1, R_2 and R_6 are as defined in Claim 1)
prepared "in situ" by reacting a vinyl-ketone (7)



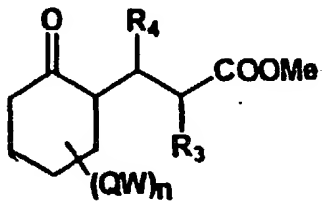
(7)

(wherein R_1, R_2, R_6 are as above defined) with a silylating agent as trimethylsilyltrifluorometansulphonic anhydride (TMSOTf) and are finally hydrolized, for example with sodium hydrogencarbonate, to give the final compound of formula (I) wherein X = O.

5. Process according to claim 4 wherein the possible introduction of the double bonds in position a or b is performed by reaction of dichlorodicianoquinone (DDQ) with the corresponding silylenolethers or by oxidation with quicksilver acetate of the saturated compound obtained as claimed above and the possible transformation of the group X is performed via the corresponding enoltriflates and following carbonylation in the presence of palladium diacetate, triphenylphosphine and the suitable nucleophilic reagent.

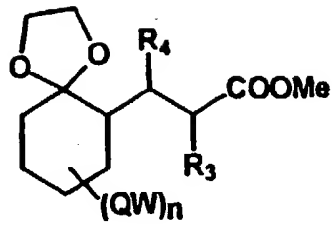
6. Process for the preparation of a compound of formula (I) according to Claim 1, wherein:

the carbonyl group of a compound of formula (2)



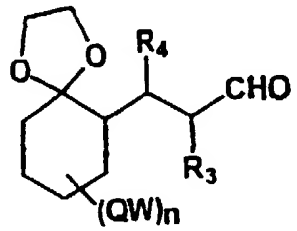
(2)

(wherein R_3, R_4, QW and n are as above defined) is protected as a ketal to give a compound (9)



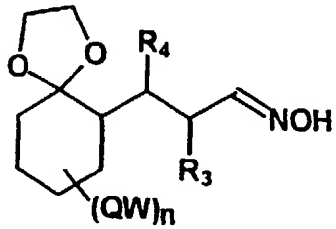
(9)

(wherein R_3, R_4, QW and n are as above defined) which is reduced to the corresponding aldehyde (10)



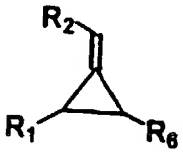
(10)

(wherein R_3, R_4, QW and n are as above defined) with DIBAL, and such aldehyde is transformed into the oxime (11)



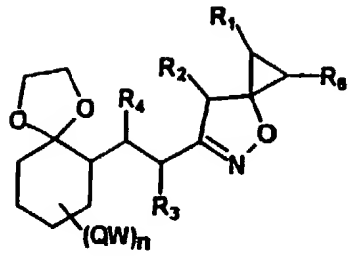
(11)

(wherein R_3, R_4, QW and n are as above defined) which is reacted with a methylenecyclopropane derivative (12)



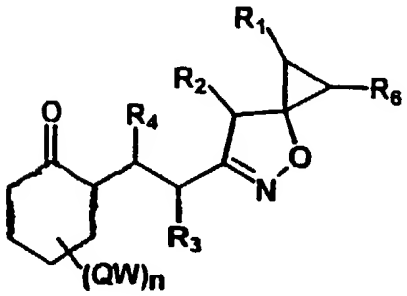
(12)

(wherein R_1, R_2 and R_6 are as above defined) to give the isoxazoline (13)



(13)

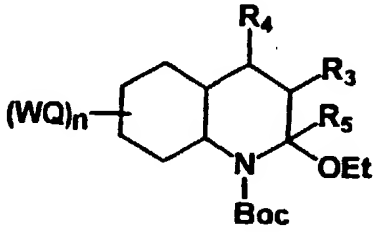
(wherein R_1, R_2, R_3, R_4, R_6, QW and n are as above defined) which is deprotected to the corresponding isoxazoline (14)



(14)

(wherein R_1, R_2, R_3, R_4, R_6, QW and n are as above defined) which is rearranged to the final product of formula (I) wherein X =O, i or h is a double bond and the other substituents are as above defined.

7. Compound of formula (6)



(6)

wherein W, Q, n, R_3, R_4, R_5 are as defined in claim 1

8. Pharmaceutical composition wherein the active principle is a compound of formula (I) according to Claim 1 or mixtures thereof in combination with the suitable pharmaceutical acceptable excipients.

9. Pharmaceutical composition according to Claim 8 for use in the inhibition of the 5αR-I and/or 5αR-II iso-emzymes.

10. Pharmaceutical composition according to claims 8 and 9 in the form suitable for topic use.

11. Method for the treatment of pathologies related to 5α-reductase enzymes by administration to the patient of a pharmaceutically active amount of a pharmaceutical composition according to Claims 7.

12. Method according to claim 11 wherein the treated pathologies are acne, baldness, prostatic cancer and prostatic hypertrophy in men and hirsutism in women.

13. Use of compounds of formula (I) according to claim 1 as inhibitors of steroid 5α-reductase enzymes in plants.

14. Agricoltural compositions for regulating the plant growth containing as active principle a compound of formula (I) according to Claim 1 or mixtures thereof possibly in combination with the additives commonly used in agricolture for this purposes.

15. Process for plant growth regulation wherein an effective quantity of a composition according to Claim 14 is distributed on the seeds and/or on the plants to treat.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 97 12 2733

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	WO 97 29107 A (APPLIED RESEARCH SYSTEMS ;GUARNA ANTONIO (IT); SERIO MARIO (IT)) 14 August 1997 * claim 1 *	1-15	C07D455/04 A01N43/42
A	EP 0 703 221 A (LILLY CO ELI) 27 March 1996 * claim 1 *	1-15	
A	WO 94 21614 A (MERCK & CO INC ;GRAHAM DONALD W (US); HAGMANN WILLIAM K (US)) 29 September 1994 * claim 1 *	1-15	
A	EP 0 591 583 A (LILLY CO ELI) 13 April 1994 * claim 1 *	1-15	
A	EP 0 591 582 A (LILLY CO ELI) 13 April 1994 * claim 1 *	1-15	
	-/--		

TECHNICAL FIELDS SEARCHED (Int.Cl.6)

C07D
A01N

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

Although claims 11 and 12 are directed to a method of treatment of the human/animal body (Article 52(4) EPC), the search has been carried out and based on the alleged effects of the compound/composition.

Place of search	Date of completion of the search	Examiner
MUNICH	15 June 1998	Gettins, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 97 12 2733

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	EP 0 532 190 A (LILLY CO ELI) 17 March 1993 * claim 1 *	1-15	
A	EP 0 531 026 A (LILLY CO ELI) 10 March 1993 * claim 1 *	1-15	
A	ACHESON R M ET AL: "ADDITION REACTIONS OF HETEROCYCLIC COMPOUNDS. PART 67. PRODUCTS FROM 1-PHENYLBUT-1-YN-3-ONE WITH VARIOUS HETEROCYCLES, AND FROM DIMETHYL ACETYLENEDICARBOXYLATE WITH SOME 2-SUBSTITUTED PYRIDINES" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, vol. 3, 1979, pages 584-590, XP002033586 Scheme 1, compound (8).	1	TECHNICAL FIELDS SEARCHED (Int.Cl.6)

EPO FORM 1503 03.82 (P04C19)

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 97 12 2733

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The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-06-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729107 A	14-08-1997	IT FI960019 A	11-08-1997
		AU 1767297 A	28-08-1997
EP 0703221 A	27-03-1996	US 5578724 A	26-11-1996
		AU 692123 B	28-05-1998
		AU 1898197 A	26-06-1997
		AU 3510295 A	09-04-1996
		CA 2158609 A	21-03-1996
		CZ 9700821 A	14-01-1998
		FI 971156 A	19-03-1997
		JP 8225533 A	03-09-1996
		NO 971248 A	18-03-1997
		PL 319163 A	21-07-1997
		WO 9609046 A	28-03-1996
		US 5622961 A	22-04-1997
		US 5622962 A	22-04-1997
WO 9421614 A	29-09-1994	AU 6413594 A	11-10-1994
		US 5621104 A	15-04-1997
EP 0591583 A	13-04-1994	NONE	
EP 0591582 A	13-04-1994	NONE	
EP 0532190 A	17-03-1993	US 5239075 A	24-08-1993
		AU 654573 B	10-11-1994
		AU 2118592 A	25-02-1993
		CA 2076479 A	22-02-1993
		CN 1071418 A	28-04-1993
		FI 923752 A	22-02-1993
		FI 964202 A	18-10-1996
		FI 964203 A	18-10-1996
		HU 68034 A	29-05-1995
		HU 9500235 A	28-08-1995
		JP 5239032 A	17-09-1993
		MX 9204817 A	01-04-1993
		NO 178542 B	08-01-1996
		NZ 244038 A	25-11-1994
		US 5334767 A	02-08-1994
		US 5495021 A	27-02-1996

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 97 12 2733

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-06-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0532190 A		US 5541190 A	30-07-1996
		US 5670512 A	23-09-1997
		US 5710163 A	20-01-1998
		ZA 9206285 A	21-02-1994
EP 0531026 A	10-03-1993	US 5250539 A	05-10-1993
		AU 2118292 A	25-02-1993
		CA 2076509 A	22-02-1993
		CN 1069488 A	03-03-1993
		FI 923751 A	22-02-1993
		HU 68064 A	29-05-1995
		JP 5213889 A	24-08-1993
		MX 9204815 A	01-12-1993
		ZA 9206286 A	21-02-1994

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82